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Expression of E-, P-, and N-cadherin and α-, β-, and γ-catenin with respect to invasion in ameloblastoma

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ABSTRACT

Ameloblastoma consists of an odontogenic epithelium and is a benign tumor without odontogenic mesenchyme. It occurs primarily in the jawbone and exhibits locally invasive growth. To clarify the factors involved in the invasion of ameloblastoma, the expression profiles of E-, P- and N-cadherin and α-, β- and γ-catenin were examined in 39 cases of ameloblastoma by immunohistochemistry. Cadherin and catenin were expressed on tumor cell membranes. Of the examined cases, 12 exhibited reduced E-cadherin expression, 12 exhibited strong P-cadherin expression, and 7 exhibited weak expression of N-cadherin. Additionally, 20 cases exhibited reduced α-catenin expression, 8 exhibited reduced β-catenin expression, and 33 cases exhibited reduced γ-catenin expression. Reduced expression of E-cadherin was associated with decreased cell adhesion, and strong expression of P-cadherin was associated with cell proliferation. Expression of N-cadherin was related to tumor invasion and suggested involvement in epithelial mesenchymal transition. In addition, reduced α-catenin in the expression region of E-cadherin suggested an abnormal function of E-cadherin. Together, these results suggest that cadherin and catenin play important roles in the development and local invasiveness of ameloblastoma.

1. Introduction

Ameloblastoma, a benign odontogenic tumor mainly occurring in the mandibular bone, invades the surrounding bone tissue and has a high risk of recurrence [1,2]. Epithelial mesenchymal transition (EMT) is considered to be related to invasion of oral tumors, since EMT-related factors are found in the invasion of ameloblastoma and oral squamous cell carcinoma (OSCC) [3,4].

E-, P-, and N-cadherin are Ca^{2+}-dependent intercellular adhesion molecules belonging to the classical cadherin family. E-cadherin is expressed on the epithelial cell membrane [5,6]. Cadherin and actin have an extracellular domain that binds to the intracellular proteins α-, β-, and γ-catenin to form a cytoskeleton [5]. Therefore, catenins play an important role in cell adhesion. Among them, β-catenin is considered to be an important molecule of the Wnt signaling pathway [7]. For each organ, α-, β-, and γ-catenin have been associated with metastasis and proliferation in oral cancer [8], thyroid cancer [9], breast cancer [10], and lung cancer [11]. Several studies have investigated the association of cadherin and catenin expression. For example, it has been reported that E-cadherin and β-catenin are involved in the development of ameloblastoma [12], and E-cadherin and α-catenin are involved in the process of cell differentiation in tooth germ [13].

The factors related to the invasion of ameloblastoma are E-cadherin and β-catenin [14], and the disappearance of these cell-cell adhesion molecules is the first event in tumorigenic ameloblastoma [15]. For example, the disappearance of the expression of E-cadherin is reported to decrease the cell adhesion function of growing ameloblastoma cells [16]. In contrast, P-cadherin is expressed in the basal cell of stratified epithelium and the basal cell layer of the placental decidua and is involved in the formation of various tissues [17]. The reduction in the expression of E- and/or P-cadherin is involved in the potential invasiveness of early OSCC [18]. Both E- and P-cadherin are expressed in parenchymal and spindle-shaped cells of the plexiform and follicular type ameloblastoma [19], and the functions of both are thought to be similar. The difference is that overexpression of P-cadherin is indicative of the invasive potential of cancer and poor prognosis of intrahepatic cholangiocarcinoma and pancreatic cancer [20]. N-cadherin is expressed in nerve tissue, myocardium, and smooth muscle cells [21,22]; it is a potential marker for early diagnosis of OSCC [23]. Expression of N-cadherin is often associated with invasiveness and motility of breast cancer cells [24]. In pancreatic cancer, overexpression of N-cadherin is involved in EMT [25].

In this study, the expression of cell adhesion molecules E-, P- and N-cadherin and intracellular α-, β- and γ-catenin was evaluated by

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Table 1
Age, gender, and site of tumor occurrence in patients with ameloblastoma.

Factor(n = 39)	
Gender	
Male	24
Female	15
Age(years)	
Mean	40
Range	7-87
Mandible	
Anterior	10
Posterior	28
Maxilla	
Anterior	0
Posterior	1
Histopathologic pattern	
Follicular	15
Plexiform	24

immunohistochemistry to clarify the local invasiveness and development of ameloblastoma.

2. Materials and methods

2.1. Materials

The biopsies and resected specimens of 39 cases of ameloblastoma (15 follicular type, 24 plexiform type) were collected at Osaka Dental University Hospital. The specimens were obtained from 24 males and 15 females, whose age ranged between 7 − 87 years with median age of 40 years. The tumor occurred in maxilla in one case and in the mandible in the remaining 38 cases. The mandibular cases were divided into 10 cases of anterior teeth and 28 of posterior (Table 1). The tissue type of ameloblastoma was classified into follicular type and plexiform type and examined. The specimens were fixed with 10% formalin and embedded in paraffin. Sections with a thickness of 2 μm were prepared, stained with hematoxylin-eosin, and immunohistochemical staining was performed. This research was approved by the Osaka Dental College Ethics Committee (approval number 110884).

2.2. Immunohistochemical staining

Paraffin sections were deparaffinized with D-limonene (Hemo-De; Scientific Safety Solvents, Keller, TX, USA) and rehydrated with graded ethanol. The sections were autoclaved (98 °C) in 10 mM citrate buffer (pH 6) for 40 min. Endogenous peroxidase activity was blocked with 3% hydrogen peroxide for 5 min at room temperature (25 °C). The sections were incubated with mouse anti-human E-, P- and N-cadherin and α-, β- and γ-catenin antibodies overnight at 4 °C (Table 2). Samples were incubated with peroxidase-conjugated dextran polymer (EnVision, DakoCytomation, Carpinteria, CA, USA) for 30 min at room temperature. Reactive products were visualized with 3,3′-diaminobenzidine (DakoCytomation) and the sections were counterstained with Mayer's hematoxylin.

Table 2
Antibodies for immunohistochemical staining BD; Becton, Dickinson and Company Transduction Lab; Transduction Laboratories.

Primary antibody	Dilution	clone	Source	Vender
E-cadherin	1:500	36	Mouse	BD
P-cadherin	1:500	56	Mouse	BD
N-cadherin	1:500	13A9	Mouse	EMD Millipore Corporation
α-catenin	1:500	5	Mouse	Transduction Lab
β- catenin	1:500	14	Mouse	BD
γ- catenin	1:1	PG5.1	Mouse	PROGEN

2.3. Double immunostaining (E-, and N-Cadherin)

Using the above-described method of immunohistochemical staining, sections were incubated with a mouse anti-human E-cadherin antibody for 40 min at room temperature. The sections were incubated with an alkaline phosphatase-conjugated anti-mouse antibody (HISTOFINE Simple Stain AP (M); NICHIREI, Osaka, Japan) as a secondary antibody for 30 min. Perma-blue (Diagnostic Biosystems, Pleasanton, CA, USA) was applied for 5 min to detect the sites of alkaline phosphatase activity. Antigen retrieval was performed in a heat bath (98 °C) in 10 mM citrate buffer (pH 6) for 40 min. Sections were then incubated with a mouse anti-human N-cadherin antibody overnight at 4 °C, followed by incubation with HISTOFINE Simple Stain AP (M) (NICHIREI) for 30 min. Perma-red (Diagnostic Biosystems) was applied for 5 min to detect the sites of alkaline phosphatase activity. Samples were washed with distilled water twice, dried well in the refrigerator, and mounted.

2.4. Evaluation of immunohistochemistry results

Immunohistochemical reactivity was assessed and samples were classified into three groups by antibodies as follows. For E-, and N-cadherin and for α-, β-, and γ-catenin, strong expression (++) was defined as expression in ≥ 50% of tumor cells; weak expression (+) was defined as expression in 10–50% of cells; and a negative (-) result was defined as expression in less than 10% of cells. On the other hand, for P-cadherin, strong expression (++) was defined as expression in ≥ 50% of peripheral cells and satellite tumor cells; weak expression (+*) was defined as expression in 10–50% of peripheral cells and some satellite tumor cells, and a negative (-) result was defined as expression in less than 10% of tumor cells.

2.5. Western blotting

The biopsies and resected tissues were lysed using a cell lysis solution (RIPA; Nacalai Tesque, Kyoto, Japan) containing protease inhibitors (Nacalai Tesque). Cell lysates were centrifuged (15,000 rpm) for 15 min to separate the supernatant. Subsequently, they were heated at 99 °C for 5 min in denaturing Laemmle buffer (Bio-Rad Laboratories, Hercules, CA, USA) and evaluated by SDS-PAGE.

The extracted proteins were electrophoresed on a 7.5% polyacrylamide gel (Bio-Rad Laboratories) for 90 min at 80 V and 0.01 A. Subsequently, the proteins were transferred onto a PVDF membrane (Bio-Rad Laboratories) for 60 min at 100 V and 0.44 A. Non-specific reactions were blocked with a blocking solution (Bullet Blocking One for Western Blotting; Nacalai Tesque) at room temperature (25 °C) for 30 min. The membranes were incubated with primary antibodies overnight at 4 °C. Samples were incubated with horseradish peroxidase-conjugated secondary antibodies and visualized using ECL detection reagent (Nacalai Tesque) (Table 3).

3. Results

3.1. Immunohistochemical staining

E-, P-, and N-cadherin and α-, β- and γ-catenin were localized in the cell membrane of stellate reticulum cells and surrounding cells of the tumor nests (Figs. 1 and 2). E-cadherin showed strong expression in 27 cases, weak expression (reduced) in 12 cases (Fig. 3), and negative expression in 0 cases. Expression of E-cadherin was observed in all cell membranes, but a reduced expression was observed in serial sections of α-catenin (Fig. 4).

Strong expression of P-cadherin was observed in 12 cases (Fig. 5), weak expression was observed in 24 cases, and negative expression was observed in 3 cases of ameloblastoma. Strong expression of N-cadherin was detected in 0 cases, weak expression was observed in 7 cases (Fig. 6), and negative expression was observed in 32 cases of

Table 3
Antibodies used for the western blot analysis BD; Becton, Dickinson and Company CST; Cell Signaling Technology.

Primary antibody	Dilution	clone	Source	Vender	Secondary antibody
E-cadherin	1:1000	36	Mouse	BD	HRP Goat anti-mouse IgG
P-cadherin	1:1000	12H6	Mouse	CST	HRP Goat anti-mouse IgG
N-cadherin	1:1000	13A9	Mouse	EMD Millipore Corporation	HRP Goat anti-mouse IgG
α-catenin	1:1000	7A4	Mouse	Zymed	HRP Goat anti-mouse IgG
β- catenin	1:1000	14	Mouse	BD	HRP Goat anti-mouse IgG
γ- catenin	1:1000	–	Rabbit	CST	Anti-rabbit IgG, HRP-Linked Antibody

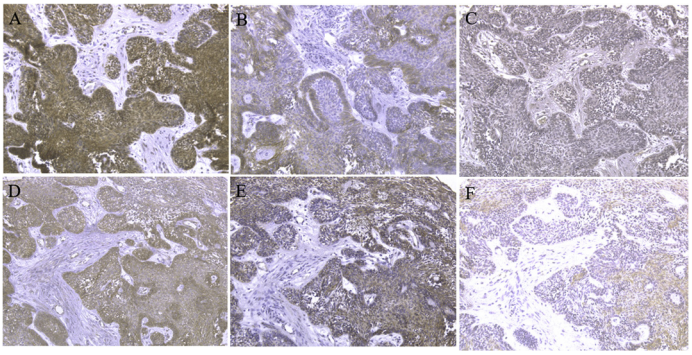

Fig. 1. Representative immunohistochemical staining patterns of (A) E-cadherin, (B) P-cadherin, (C) N-cadherin, (D) α-catenin, (E) β-catenin, and (F) γ-catenin in plexiform type ameloblastoma (×200) E- and P-cadherin and α-, β-, and γ-catenin were all expressed in the cell membrane, while N-cadherin was not. P-cadherin was expressed in peripheral cells in tumor nests.

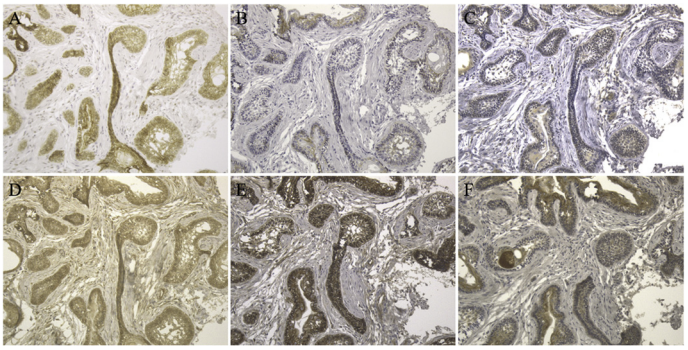

Fig. 2. Representative immunohistochemical staining patterns of (A) E-cadherin, (B) P-cadherin, (C) N-cadherin, (D) α-catenin, (E) β-catenin, and (F) γ-catenin in follicular type ameloblastoma (×200) E- and P-cadherin and α-, β-, and γ-catenin were all expressed in the cell membrane, while N-cadherin was not. P-cadherin was expressed in peripheral cells in tumor nests.

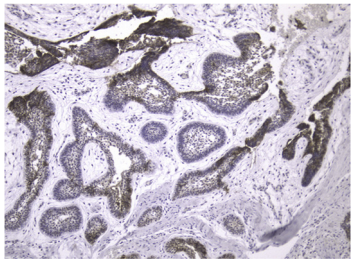

Fig. 3. Immunohistochemical staining results for E-cadherin in follicular type ameloblastoma (×100) Strong E-cadherin expression was observed in peripheral cells of the tumor nest, and reduced expression was observed in stellate cells of the tumor nest.

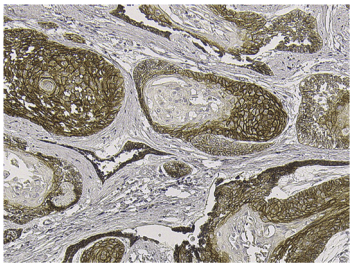

Fig. 5. Immunohistochemical staining results for P-cadherin in follicular type ameloblastoma (×20) P-cadherin strong expression was observed in the membranes of peripheral cells, stellate cells, and squamous metaplastic cells.

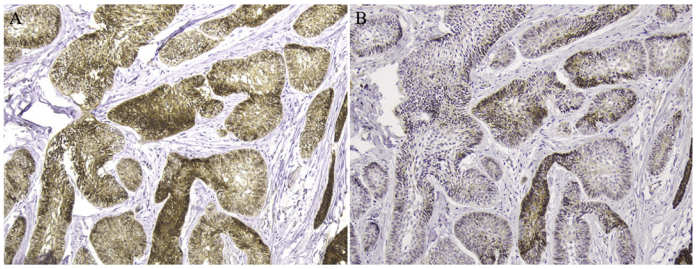

Fig. 4. Immunohistochemical staining results for (A) E-cadherin and (B) α-catenin in follicular type ameloblastoma (×100) E-cadherin expression was observed in all cells, but the expression of α-catenin was reduced.

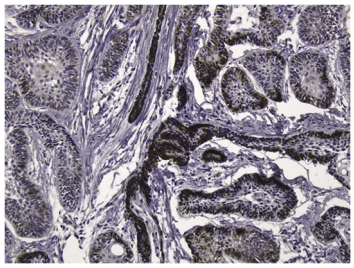

Fig. 6. Immunohistochemical staining results for N-cadherin in follicular type ameloblastoma (×200) Expression of N-cadherin was observed in the cell membranes of many tumor cells.

Table 4
Staining results of E-, P-, and N-cadherin and α-, β- and γ-catenin in ameloblastoma.

	Follicular(n = 15)	Plexiform(n = 24)	Statistics(P value)
E-cadherin			
+ +	12	15	
+	3	9	P = 0.51
−	0	0	
P-cadherin			
+ +	4	8	
+ *	9	15	P = 0.56
−	2	1	
N-cadherin			
+ +	0	0	
+	5	2	P = 0.141
−	10	22	
α-catenin			
+ +	10	9	
+	5	10	P = 0.08
−	0	5	
β-catenin			
+ +	13	18	
+	2	6	P = 0.57
−	0	0	
γ-catenin			
+ +	2	4	
+	9	11	P = 0.68
−	4	9	

ameloblastoma. Strong expression of α-catenin was observed in 19 cases, weak expression was observed in 15 cases, and negative expression was observed in 5 cases of ameloblastoma. Strong expression of β-catenin was detected 31 cases, weak expression was observed in 8 cases, and negative expression was observed in 0 cases of ameloblastoma. Strong expression of γ-catenin was detected in 6 cases, weak expression was observed in 20 cases, and negative expression was observed in 13 cases of ameloblastoma (Tables 4 and 5). Seven cases showed expression of both N-cadherin and E-cadherin.

There was no difference between the cases in the expression of all follicular type and plexiform type in ameloblastoma.

3.2. Double immunostaining

The expression of N-cadherin was elevated in the regions where E-cadherin expression was decreased (Fig. 7).

3.3. Western blotting

E-, P-, and N-cadherin and α-, β-, and γ-catenin were detected, as evidenced by bands of 120, 120, 140, and 102, 92, and 83 kDa, respectively (Fig. 8).

4. Discussion

Ameloblastoma is a typical benign odontogenic tumor that occurs in the jawbone, but shows local invasiveness and is difficult to treat. The expression of cell adhesion molecules E-, P- and N-cadherin and α-, β- and γ-catenin are considered to be different between ameloblastoma and normal tissue. To clarify the relationship between this differential expression pattern and the invasion of ameloblastoma, the expression of cadherin and catenin was studied by immunohistochemistry for 39 cases of ameloblastoma.

In the present study, E-cadherin was expressed in all 39 cases, but 12 cases had a weak (reduced) expression (Table 4). Siar et al. reported that reduced E-cadherin expression decreases tumor cell adhesion [16]. Furthermore, E-cadherin expression was found to be reduced in ameloblastoma, OSCC with metastasis, and OSCC invasive frontal line [3,8,19]. There are reports that reduced E-cadherin expression is associated with tumor progression [26]. Mahomed et al. reported that the disappearance of E-cadherin and β-catenin is a marker of metastasis in OSCC [8]. Chaw et al. also suggested that the expression of EMT markers (E-cadherin, β-catenin, APC, and vimentin) is affected by dysregulation of the Wnt pathway [27].

N-cadherin is found in various tumors related to EMT. Expression of N-cadherin is associated with the invasion and motility of breast cancer cells [24]. In pancreatic cancer, overexpression of N-cadherin is involved in EMT and is affected by various growth factors [25]. From these reports, we predicted that N-cadherin expression will be present contrary to the reduced expression of E-cadherin in EMT; however, in our study, all 7 cases exhibiting N-cadherin expression were cases that exhibited E-cadherin expression (Table 5). There may be a temporal difference in their expression such that N-cadherin is expressed earlier and a weak E-cadherin expression occurs later. Conversely, 12 cases of weak E-cadherin expression were cases in which N-cadherin was not expressed (Table 5). Even if N-cadherin is expressed, it may be evaluated as unexpressed depending on the position where the section is taken; therefore, 12 of these cases may underestimate the expression of N-cadherin. In the double immunostaining, strong N-cadherin staining in the portions showing weak E-cadherin expression confirmed that E-cadherin expression is downregulated concomitantly with the upregulation of N-cadherin expression (Fig. 7).

P-cadherin is highly expressed in the placenta [28] and is expressed in the cell membrane of the basal cell layer in normal squamous epithelium of the oral mucosa [17]. A previous report showed that overexpression of P-cadherin promotes the invasive ability of cancer [29] and poor prognosis of intrahepatic cholangiocarcinoma or pancreatic cancer, and depending on the tumor, it may be useful as a biological marker [18,20]. Saito et al. reported that both E- and P-cadherin are expressed in parenchymal cells in plexiform type and spindle-shaped cells in follicular type in ameloblastoma [19]. In contrast, in our study, E-cadherin was expressed from peripheral cells to satellite cells, whereas P-cadherin was expressed in the peripheral cells of tumor nests in plexiform-type and follicular-type in ameloblastoma.

There are various reports on catenin; the expression of α-catenin is correlated with the expression of E-cadherin and the attenuation of expression is related to the invasive function [15]. Further, E-cadherin, α-catenin, and β-catenin are involved in the metastasis of oral cancer [30]. E-cadherin and β-catenin were also weakly expressed in both ameloblastoma and ameloblastic carcinoma [31]. Weak expression of β-catenin and γ-catenin and a reduced expression of P-cadherin have also been observed in ameloblastic carcinoma [32].

In this study, when focusing on 7 N-cadherin positive cases, in which EMT was thought to have occurred, two cases with reduced expression of α-catenin out of three cases with strong P-cadherin expression and a strong expression of α-catenin in three cases with weak P-cadherin expression were observed. Therefore, when analyzing the relationship between P-cadherin and α-catenin in all cases, α-catenin reduced cases were 0 (0%) in 3 cases with P-cadherin negative

Table 5
Staining intensity and histopathological classification of E-, P-, and N-cadherin and α-, β- and γ-catenin in ameloblastoma.

Case no.		E-cadherin	P-cadherin	N-cadherin	α-catenin	β-catenin	γ-catenin
1	P	+ +	+ +	-	+ +	+	+
2	P	+ +	+ +	+	-	+ +	+ +
3	F	+ +	+ +	+	+	+ +	+
4	F	+ +	+ +	+	+ +	+ +	+
5	F	+ +	+ +	-	+	+	-
6	P	+ +	+ +	-	+	+ +	+
7	P	+ +	+ +	-	+	+ +	+
8	P	+ +	+ +	-	+	+ +	-
9	P	+ +	+ +	-	+ +	+ +	+ +
10	F	+ +	+ +	-	+ +	+ +	+ +
11	P	+ +	+ *	-	+ +	+ +	+
12	P	+ +	+ *	-	+ +	+ +	+
13	F	+ +	+ *	-	+ +	+ +	+
14	F	+ +	+ *	+	+ +	+ +	+
15	F	+ +	+ *	+	+ +	+ +	+
16	F	+ +	+ *	+	+ +	+ +	+ +
17	P	+ +	+ *	-	+	+	+
18	P	+ +	+ *	-	+	+ +	-
19	P	+ +	+ *	-	+	+ +	-
20	F	+ +	+ *	-	+	+ +	+
21	P	+ +	+ *	-	+ +	+ +	+
22	P	+ +	+ *	-	+ +	+ +	+
23	P	+ +	+ *	-	+ +	+ +	+
24	F	+ +	+ *	-	+ +	+ +	-
25	F	+ +	-	-	+ +	+ +	-
26	P	+ +	-	+	+ +	+ +	+
27	F	+ +	-	-	+ +	+ +	+
28	P	+	+ +	-	-	+ +	-
29	P	+	+ +	-	-	+ +	-
30	P	+	+ *	-	-	+	-
31	F	+	+ *	-	+ +	+ +	+
32	P	+	+ *	-	-	+ +	+
33	P	+	+ *	-	+	+	-
34	P	+	+ *	-	+	+	-
35	F	+	+ *	-	+	+	-
36	P	+	+ *	-	+	+	+ +
37	P	+	+ *	-	+	+ +	-
38	F	+	+ *	-	+	+ +	+
39	P	+	+ *	-	+ +	+ +	+ +

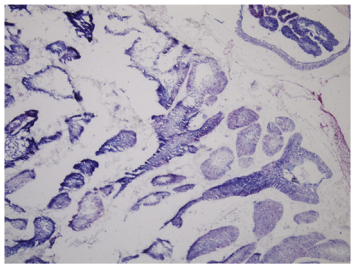

Fig. 7. Double-immunostaining results for N-cadherin and E-cadherin (×100) in the follicular type N-cadherin staining is shown in red and E-cadherin staining is shown in blue. The expression of E-cadherin was reduced in the region with increased N-cadherin expression. P; Plexiform type F; Follicular type.

expression, 12 (50%) in 24 cases with P-cadherin weak expression, and 8 (66.7%) in 12 cases with strong P-cadherin expression (Table 5). Thus, α-catenin expression tended to reduce with strong P-cadherin expression and this tendency was observed for only α-catenin among the catenins.

In this study, we compared and examined a part of serial sections in one organization. Evaluation may be different depending on the position where the section is taken, as described above. Similar examination on a tumor tissue and all its serial sections would allow us to obtain more information and may be useful in elucidating the properties of ameloblastoma in the future.

5. Conclusion

Our data suggest that reduced E-cadherin expression, P-cadherin strong expression, N-cadherin weak expression, and a reduced α-catenin expression impart invasive potential to ameloblastoma. It is necessary to increase the number of cases studied and to verify the

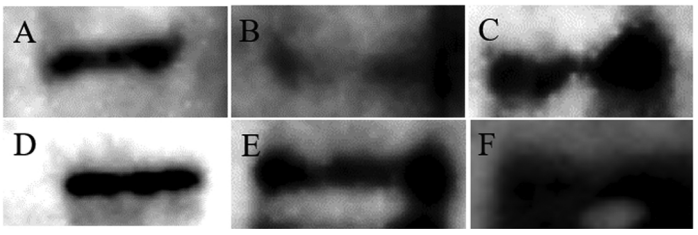

Fig. 8. Western blot analyses of (A) E-cadherin, (B) P-cadherin, (C) N-cadherin, (D) α-catenin, (E) β-catenin, and (F) γ-catenin in ameloblastoma The immunoreactive bands for E-cadherin, P-cadherin, N-cadherin, α-catenin, and β-catenin were 120 kDa, 120 kDa, 140 kDa, 102 kDa, 92 kDa, and 83 kDa, respectively.

function of these proteins.

Conflict of interest

No potential conflict of interest to disclose.

Acknowledgments

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